STUDYING THE BIOCHEMICAL AND PSYCHOSOMATIC ASPECT OF DRIVERS' FATIGUE

A Thesis Submitted In Partial Fulfillment

Of the requirement for the degree of

Bachelor of Technology

Biotechnology

By

Biswajit Maharathi

107BT005

Department Of Biotechnology and Medical Engineering

National Institute of Technology, Rourkela

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Under guidance the of

Dr. B.P. Nayak

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2011

Dr. B.P. Nayak
Professor
Dept. of Biotechnology and
Medical Engineering,
National Institute of technology,
Rourkela, 769008

Phone No- (O) 0661-2462287
(R) 0661-2463287
Mail ID: bibhukalyan@nitrkl.ac.in
bibhu2011@gmail.com

Certificate

This is to certify that the work in the thesis entitled ***"studying the biochemical and psychosomatic aspect of drivers' fatigue"*** by ***Biswajit Maharathi*** in partial fulfillment of the requirements for the award of the degree of Bachelor of Technology in Biotechnology Engineering in the department of Biotechnology and Medical Engineering, National Institute of Technology Rourkela is an authentic research work carried out by him under my supervision and guidance.

To the best of my knowledge, the matter embodied in the report has not been submitted to any other University/Institute for the award of any Degree or Diploma.

Date: 13/ May/2011
Place: Rourkela

Dr. Bibhukalyan Prasad Nayak
Asst. Professor
Dept. of Biotechnology and Medical Engineering
NIT Rourkela-769008, Odisha

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(Biswajit Maharathi)

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Abstract

Central fatigue out of prolonged monotonous task and sleep deprivation in drivers accounts for majority of road-traffic accidents. This necessitates a precise staging of drivers' fatigue in real time. The intent of this current study is to evaluate the overall fatigue in drivers by observing the variation of a series of biochemical and subjective parameters during simulated driving condition comprising monotonous task and sleep deprivation. Briefly, 12 well trained healthy drivers were subjected to simulated driving environment for a period of 16 hours with one night sleep deprivation. During the whole course of experiment, blood samples were collected at an interval of 5 hours and were analyzed for various biochemical parameters including random blood sugar, blood urea, serum creatinine, triglyceride, cholesterol and total protein content. In addition, the extent of fatigue was quantified by some subjective assessment such as SF36v2 Health Survey Scoring, Beck Depression Inventory and Oswestry Disability Questionnaire. All these parameters (both biochemical and subjective) gradually increased with the progress of fatigue. The subjective assessments concluded a substantial decline in health (both physical and mental) and a significant increase in depression level with the progression of fatigue. It was concluded that a combined result of biochemical parameters and subjective assessment can be utilized in clinical staging of fatigue.

Key Words: central fatigue, sleep deprivation, creatinine, triglyceride, depression.

Chapter -1

Introduction

Introduction

Fatigue from physiology point of view can be defined as the decreased capability or complete inability of an organism, an organ, or a part to function normally because of excessive stimulation or prolonged exertion [1]. Fatigue has a very complex origin, having a combined influence of events occurring in both periphery and central nervous system [4]. Accordingly fatigue has been divided in two components namely Physical fatigue or peripheral fatigue (PF) which occurs due to muscular dysfunction and central fatigue (CF) which occurs due to specific alterations in the central nervous system. The physical fatigue is a normal result of overstimulation, active recreation, and physical exertion etc., where as the central fatigue originates due to stress, workloads, depression, boredom, sleep deprivation etc. Even if both the terms seem to be dissimilar, it is quite difficult to differentiate both. The central fatigue starts at molecular level much prior to the symptoms appears. The study published in many journals says CF appears due to certain neurotransmitters among which Serotonin or 5-HT (5-hydroxytryptamine) is the most studied one. There are many literatures that suggest hypothesis for the genesis of CF among which Central Fatigue hypothesis proposed by E. Blomstrand is one of the most accepted versions [15]. This hypothesis is supported by many researchers in the later period. According her, during prolong exercise; there is an uptake of almost all amino acids along with branched chain amino acid (BCAA) by the muscle. This results in a decreased level of BCAA in plasma. Due to the decreased glycogen level, to fulfill the energy requirements, free fatty acid is released by adipose tissue. Since free fatty acid has more affinity for albumin, it replaces some of the tryptophan molecules bound to albumin (Curzon et al., 1973) [16] resulting an increase in plasma free tryptophan level. This results in an increased plasma free

tryptophan/BCAA level which in turn increased the amount of tryptophan crossing the blood brain barrier. Tryptophan is a precursor molecule for the synthesis of serotonin, hence plays an important role by synthesis, concentration and release of 5-HT in the brain (Newsholme, 1986) [17]. This brain 5-HT is involved in control of sleepiness, arousal and mood, hence linked with the central fatigue during sustained exercise.

After prolong CF, distortion in the peripheral metabolism starts, due to improper commands from brain, which initiates peripheral fatigue (PF). Again PF releases certain waste products that in turn add to the CF. In this manner both the fatigue components act in a vicious manner. So after certain period of induced CF; peripheral blood parameter can suitably represent the stages of CF. CF can have many diverse origins out of which sleep deprivation is one of the major cause which can impair brain activities as much as alcohol can. Sleep is a fundamental restorative process for the nervous system. Severe impairments of the operator's ability to perceive, recognize, and respond to emergencies and unanticipated events can occur with the disruption of this homeostatic drive [2]. This has increased a risk of mishaps in military, aviation as well as road transportation sector. Hence establishing a comparative study of sleep deprivation on human performance is essential in order to develop mitigation strategies to counter fatigue.

Chapter-2

Literature Survey

Literature Survey

Driver's fatigue is one of the major problems in transport systems. According to a study done by Harvard Medical School, it was found that 28% of the adult drivers actually fallen asleep during driving whereas around 54% of the drivers had feeling of drowsiness on wheels. The National Highway Traffic Safety Administration reports 1.55% death rate and 40% injury annually due to drowsy driving. Report by Sleep Research Centre says 20% of the major serious road accidents are caused due driver's fatigue i.e. falling asleep at the wheel in Great Britain [3]. A study in USA says 50% road accidents on two of America's busiest roads were fatigue related [4]. In support to this another study says 30-40% of road accidents involving heavy vehicles are caused by driver sleepiness [5]. An Australian road safety organization estimates that 6% of road mishaps, 15% fatal accidents and 30% fatal crashes were due to driver's fatigue. World Health organization report in 2009 says more people die in India due to road accidents than anywhere else in the world.

Studies in various countries say young male drivers (age 25 ± 5) are more prone to sleep related crash due to their tight schedule and tendency to drive high mileage on freeways. While considering the time of Day the results are even more interesting. It was found that sleep related accidents were peak in the early hours (between 02:00 Hrs – 06:00 Hrs). According to study done by Horne, it was found that the drivers were 50 times more prone to fall asleep at wheel at 02:00 Hrs than at 10:00 Hrs [6]. It was also found that in case of long journey on monotonous roads the probability of falling asleep is more. Recent research in New Zealand suggests that staying for 17-19 hours awake results the equivalent level of impairment in brain function as drinking of around 50 ml of alcohol induces [7].

Monotonous exercise with sleep deprivation, particularly driving over prolonged period can induce fatigue which is developed with gradual increase in cerebral metabolism [9-11]. Various blood biochemical parameters particularly the neurotransmitters and their metabolic products, blood glucose, urea, creatinine, triglyceride, total protein content in blood represents either the inducer or the outcome of the events leading to fatigue. These parameters can reliably reflect the gradual genesis and progression of fatigue.

Apart from the blood biochemical parameters, the subjective assessment of the individuals can also reflect the level of fatigue. The Beck depression inventory reflects the gradual increase in the depression and languorous along with the progression of fatigue. Apart from this SF36v2 health survey and Oswestry disability questionnaire give the variation of mental as well as physical health parameters along with fatigue genesis and its subsequent staging.

In this work an attempt has been made to simultaneously measure the various blood biochemical parameters and subjective measurement. In each type of measurement multiple factors have been analyzed and their relation with fatigue progression has been evaluated.

Chapter-3

Materials and Methods

This chapter describes the materials, methodology and the protocols followed for the estimation of the biochemical parameters, the set up of the simulator for the fatigue study.

3.1 Materials

All the assay kits used for the analysis of the various biochemical parameters are certified for IVD (in vitro diagnosis). The Glucose Kit, Urea Kit, Creatinine Kit, triglyceride Kit, Cholesterol Kit were procured from CREST BIOSYSTEMS; total protein assay kit was procured from AutoZyme, ACCUREX biomedical Pvt. Ltd.; and the CK-MB kit was procured from CHEMELEX, S.A. The blood collection tubes and disposable syringe were obtained from BD BIOSCIENCES (India). For the colorimetric analysis of the blood sample, a semi automated biochemical analyzer (EVOLUTION 3000) was used.

3.2 Simulator Setup

The simulator consist of a PC (specification), truck simulator software (EURO TRUCK), a software compatible steering wheel (900º rotation) with a vibration leg pad and hydraulic brake system (Driving Force GT, Logitech, India), an LCD projector, a HD Sound system(INSPIRE M 4500™, CREATIVE) and a screen. The simulator module along with the audio visual unit was installed in the PC. The projector and the screen were placed in such ways that, the driver can get a clear visibility. The whole setup was arranged keeping drivers ergonomics in point of view.

3.3 Subjects

Twelve healthy male human individuals of different age group (39.2±12.3 SD) who were trained with heavy vehicle driving were hired from the Regional State transport Division located at

Sector-2, Rourkela, Odisha. Since drivers fatigue is a result of several factors such as irregular driving schedule, long time driving, sleep deprivation, mental and psychological conditions etc, and the similar conditions were simulated in the laboratory environment by articulating volunteers to undergo monotonous exercise with sleep deprivation. Prior to the experiments, the subjects were undergone strict clinical examination by registered medical practitioner and were declared healthy. An informed consent in written form was obtained from each subject. Their blood samples were collected in periodic intervals for the estimation of various blood biochemical parameters to get the genesis and progressive stages of fatigue development.

3.4 Experimental Design

The experiment was conducted under laboratory stimulatory conditions with two subjects in a single session. The entire experiment was subdivided into multiple stages (for every individual, starting time of different stages were Day-1: Stage1- 18:00Hrs, stage2-00:00Hrs; Day-2: Stage3-05:00 Hrs, stage4-10:00 Hrs), and in each stage the individual was asked to perform virtual driving on simulator to generate mental as well as visual fatigue. Prior to the experiment the individuals were asked to perform their normal day to day activity except certain activities like sleeping in the afternoon, any consumption of alcohol, caffeine, and tobacco etc. Just before the start of the experiment (18:00 Hrs), each participant was subjected to a series of questionnaire for their subjective assessment before induction of any fatigue. In addition, the first blood sample was collected (that serves as the control) followed by a predesigned snacks. The subjects were kept awake during the whole session of the driving simulation. The successive blood samples were collected at 00:00Hrs, 05:00Hrs, and 10:00 Hrs to observe the effect of fatigue on biochemical parameters. At the same time the subjective assessment was also repeated at the

same time points of blood collection. They were also made to undergo monotonous exercise at regular intervals thus with sleep deprivation and monotonous exercise an artificial fatigue condition was simulated *in vitro.*

Time points	18:00 Hours DAY-1	21:00-22:00 Hours DAY-1	00:00 Hours DAY-2	05:00 Hours DAY-2	10:00 Hours DAY-2
Analysis: 1. Biochemical parameters 2. Subjective assessment		Dinner Break	Analysis: 1. Biochemical parameters 2. Subjective assessment		
Subject : 12 Healthy Human beings					

3.5 Blood Sample Collection

The blood sampling was done four times throughout the experiment from all the individuals. Briefly a tourniquet was wrapped around either arm (left or right arm altering at each time point) of the individual and was asked to flex the elbow as well as the fingers. From the anterior region of the elbow, 5ml of blood was collected by puncturing the brachial vein through 5ml disposable syringe fitted with 22G needles (BD Biosciences, India) after sterilizing it with a cotton swab soaked with 70% alcohol. 2ml of the blood was collected in a tube containing clot inhibitor (Na-EDTA) to obtain whole blood, and the remaining 3ml was collected in tubes containing clot activator(coated with Silicone gel,AkuSet™,Eastern Medikit Limited) to obtain serum, for the biochemical and the immunological assays. The samples were vortexed 8 times for proper

mixing followed by preservation in refrigerator at 2-8ºC.Later the samples were analyzed for various blood biomarkers.

3.6 Measurement of Blood Biomarkers

The blood sample was centrifuged at 3200 rpm for 12minutes and then the plasma was collected. The estimation was done by the help of semi-automated Biochemical Analyzer (Evolution 3000) using marketed kits. (Crest Diagnostics).

3.6.1 Glucose assay

3.6.1.1 Procedure

Wavelength/filter : 505nm/green

Temperature : 37ºC

3.6.1.2 Sample preparation

Three clean and dry test tubes were taken and marked Blank (B), Standard(S), and Test (T). Then the sample and the reagents were added in the following sequence.

Addition sequence	B (ml)	S(ml)	T(ml)
Glucose Reagent (L1)	1.0	1.0	1.0
Distilled Water	0.01	-	-
Glucose Standard(S)	-	0.01	-
Sample	-	-	0.01

All the mixtures were mixed well and incubated at 37ºC for 10minutes. Then the absorbance was measured.

3.6.2 Urea Assay

3.6.2.1 Procedure

Wavelength/Filter : 570 nm/ yellow

Temperature : 37ºC

3.6.2.2 Sample Preparation

Three clean and dry test tubes were taken and marked Blank (B), Standard(S), and Test (T).

Then the sample and the reagents were added in the following sequence.

Addition Sequence	B(ml)	S(ml)	T(ml)
Buffer Reagent	1.0	1.0	1.0
Enzyme Reagent	0.1	0.1	0.1
Distilled Water	0.01	-	-
Urea standard	-	0.01	-
Sample	-	-	0.01
The above preparation was mixed well and incubated for 5min. at 37ºC			
Chromogen reagent(L3)	0.2	0.2	0.2

Again the preparation was mixed well and was incubated for 5min. at 37ºC and then the absorbance was measured.

3.6.3 Creatinine assay

The blood sample with coagulant was taken and the serum was separated. This was centrifuged at 3200 rpm for 12minutes and then the serum was collected. The estimation was done by the help of semi-automated Biochemical Analyzer (Evolution 3000) using marketed kits. (Crest Diagnostics).

3.6.3.1 Procedure

Wavelength/filter : 520nm/green

Temperature : 30ºC/37ºC

3.6.3.2 Sample Preparation

Two clean and dry test tubes were taken and marked as Standard(S), and Test (T).

Then the sample and the reagents were added in the following sequence.

Addition sequence	(S)/(T) 30ºC/37ºC	(T) in ml 30ºC/37ºC
Picric Acid Reagent	0.5 ml	0.5 ml
Buffer Reagent	0.5 ml	0.5ml
Creatinine Standard (S)	0.1 ml	0.1 ml

The preparation was mixed well and the first absorbance was taken exactly after 30secs and the second one was taken exactly after 60 sec. since it's a semi-automated analyzer the whole thing was programmed.

3.6.4 Triglycerides Assay

3.6.4.1 Procedure

Wavelength/Filter: 505nm/Green

Temperature: 37ºC

3.6.4.2 Sample preparation

Three clean and dry test tubes were taken and marked Blank (B), Standard(S), and Test (T).

Then the sample and the reagents were added in the following sequence.

Addition sequence	B (ml)	S(ml)	T(ml)
Working Reagent	1.0	1.0	1.0
Distilled Water	0.01	-	-
Triglycerides Standard(S)	-	0.01	-
Sample	-	-	0.01

The above preparations were mixed well and incubated at 37ºC for 5 min. Then the absorbance was measured.

3.6.5 Cholesterol Assay

3.6.5.1 Procedure

Wavelength/Filter: 505nm/Green

Temperature: 37ºC

3.6.5.2 Reagent Preparation

The two reagents L1 and L2 were mixed in a 4:1 ratio. This works as a working reagent.

3.6.5.3 Sample preparation

Three clean and dry test tubes were taken and marked Blank (B), Standard(S), and Test (T).

Then the sample and the reagents were added in the following sequence.

Addition sequence	B (ml)	S(ml)	T(ml)
Working Reagent	1.0	1.0	1.0
Distilled Water	0.01	-	-
Cholesterol Standard(S)	-	0.01	-
Sample	-	-	0.01

The above preparations were mixed well and incubated at 37ºC for 5 min. Then the absorbance was measured.

3.6.6 Total Protein Assay

3.6.6.1 Procedure

Wavelength: 546nm (530-570 nm)

Temperature: 25-30ºC

3.6.6.2 Sample preparation

Three clean and dry test tubes were taken and marked Blank (B), Standard(S), and Test (T).

Then the sample and the reagents were added in the following sequence.

Addition sequence	B (ml)	S(ml)	T(ml)
Working solution	1.0	1.0	1.0
protein Standard	-	0.01	-
Sample	-	-	0.01

The above preparations were mixed well and incubated at 37ºC for 5 min. Then the absorbance was measured.

3.7 Subjective assessment

The subjective assessment for fatigue is based on a set of questionnaires which were asked to each subject at the end of each step. For this assessment three standard protocols were followed namely SF36 V2 health survey that scores the individual general health status and related quality of mental and physical status during the task/disease/intervention; Beck Depression Inventory (BDI-II), which consists 21 multiple choice self reportable questions, have a basic motto to estimate the severity of depression and detachment from the current task in the subject; Oswestry Disability Questionnaire which is basically used to determine the extent of pain and disability out of an intervention. All these assessment instruments were slightly modified as per the requirement of the current study and the details are supplied in appendix-I.

The questions were asked through an interactive session and the scoring was done on the combined view of the subject's self assessment and the observation of one of the member of the research team.

3.7.1 SF36v2 questionnaire

SF36v2® Health Survey is a set of questionnaires designed by Quality Metric Inc. which gives valid information about functional Health of an individual. This generic health survey can be used across age groups, diseases, and is appropriate for a wide variety of applications worldwide. This SF36v2® Health Survey asks 36 questions to measure the functional health and the well-being from the patient's point of view [12]. The survey is meaningful to clinicians, researchers, and administrators across the health care spectrum [12]. This has various applications which include assessing treatment effectiveness, measuring health improvement or decline, comparing health factors across population etc. The detail information has been provided in Appendix-I.

3.7.2 Beck Depression Inventory

Beck Depression Inventory invented by Beck, is a set of questionnaire used for the assessment of depression level in patients, professionals etc. The recent version BDI-II is a generic instrument that can be used across age groups above thirteen, and is composed of questionnaires that relate to depression level (hopelessness, irritability etc.) , cognitions (guilty feeling, feeling of being punished etc.) as well as physical symptoms [13]. The details of the questionnaire section is provided in appendix-I.

3.7.3 Oswestry Disability Questionnaire

This is one of the extremely important tools that researchers and clinicians use to measure patient's permanent disability. This ten questionnaire section gives us the information of how the body pain affects the ability to manage the day to day life.

Chapter-4

Results and Discussion

The result section is divided in two parts.

1. Blood Biochemical measures
2. Subjective assessment Results

4.1 Blood biochemical measures

4.1.1 Glucose level in whole Blood

The average value of the blood glucose level (RBS) in the subjects gradually increased in accordance with level of fatigue and the duration of the sleep deprivation i.e. Stage1: 94.23 ± 2.24, Stage2: 104.85 ± 2.07, Stage3: 125.15 ± 2.86, Stage4: 107.77 ± 1.63 (Figure-1) . However, RBS at 4th time point (10:00 hrs) of the second day followed by one night of sleep deprivation decreased. This indicates RBS reached maximum at the peak of sleep debt.

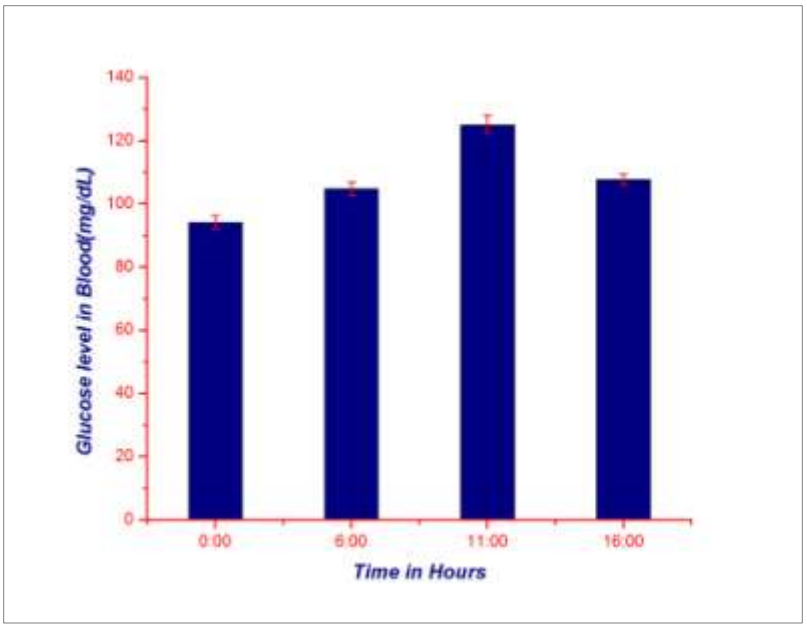

Figure-1: Average Random Blood sugar (RBS) level

Earlier researchers have found profound alteration in the glucose metabolism during sleep deprivation. Studies say, during highest of the sleep debt, the subjects took 40 percent longer

duration to regulate their blood sugar level following an injection of glucose. The ability to secret insulin was decrease about 30 percent [14].

4.1.2 Creatinine level in serum

The creatinine level increased proportionately with the duration of sleep deprivation (Figure-2). The end point result shows an increased concentration of creatinine which above the normal cutoff signifying that kidney functions might be compromised.

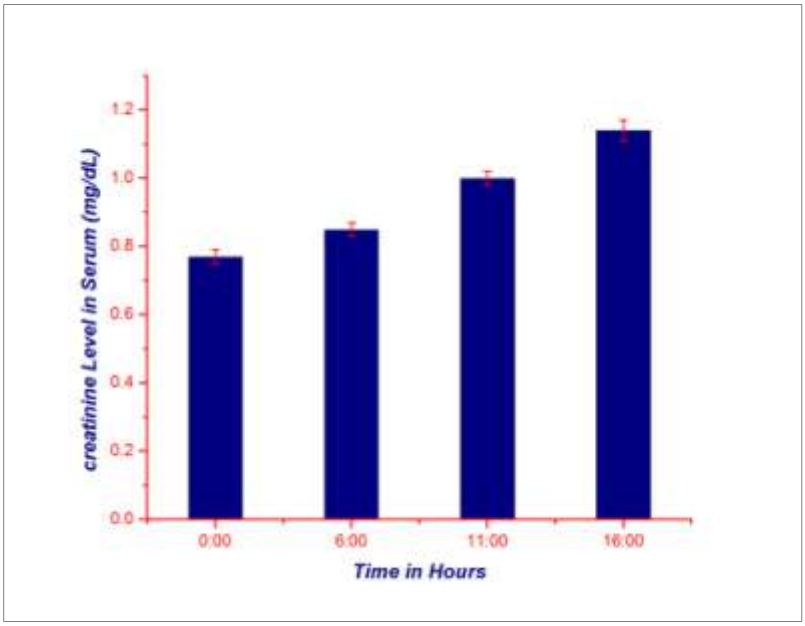

Figure-2: Creatinine level in Serum

The increased creatinine concentration is a significant parameter of peripheral fatigue that involves muscle atrophy which in turn might have surcharged the kidneys. The increase in this peripheral indicator of fatigue can be explained by spread of persistent central fatigue to the periphery which in turn leads to the degradation of muscle protein. At the same time, various amino acids are also produced from protein catabolism along with tryptophan that crosses BBB to aggravate central fatigue, generating a vicious cycle [18-20].

4.1.3 Urea level in Blood

The blood urea level also showed an increasing trend with the progression of fatigue as depicted in the figure-3.

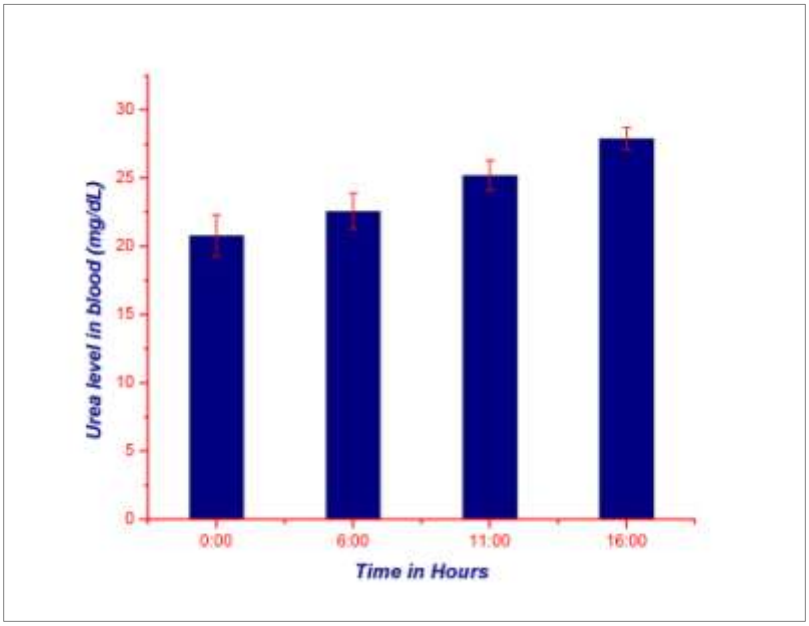

Figure-3: Urea Level in Blood

The more logical way of expressing blood urea is the form of Blood Urea nitrogen (BUN). BUN (normal range=7-21 mg/dL) is the measure of amount of nitrogen in the blood present in the form of Urea and is a measurement of renal function. The trend in BUN, that was estimated from the blood urea level [BUN= Urea (mg/dL) / 2.14] showed obviously the same trend as that of blood urea (Figure-4).

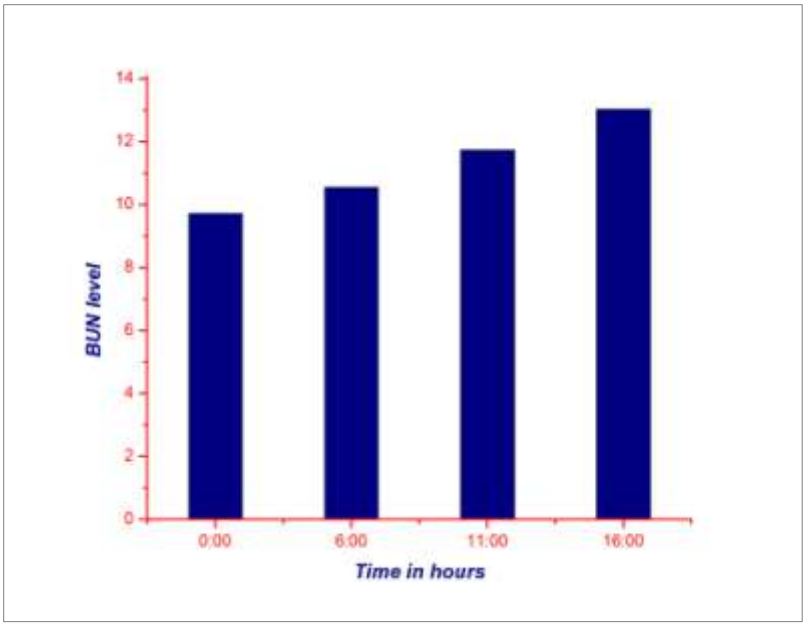

Figure-4: Blood Urea Nitrogen Level

A regular elevation in blood Urea level as well BUN in the course of experiment may suggest either increased protein catabolism to supply energy needs as observed and reported in conditions of sleep deprivation [21] or it may suggest the impaired renal function (since the subjects were healthy and had no systemic abnormalities verified by clinical examinations, obviously this is not the case). Moreover, an elevated BUN level in the scenery of relative normal creatinine concentration may reflect a physiological situation of a relative decrease of blood flow to the kidney without indicating any kidney dysfunction. Thus BUN to serum creatinine ratio acts as a clinically significant indicator of kidney function which has been shown in Figure-5.

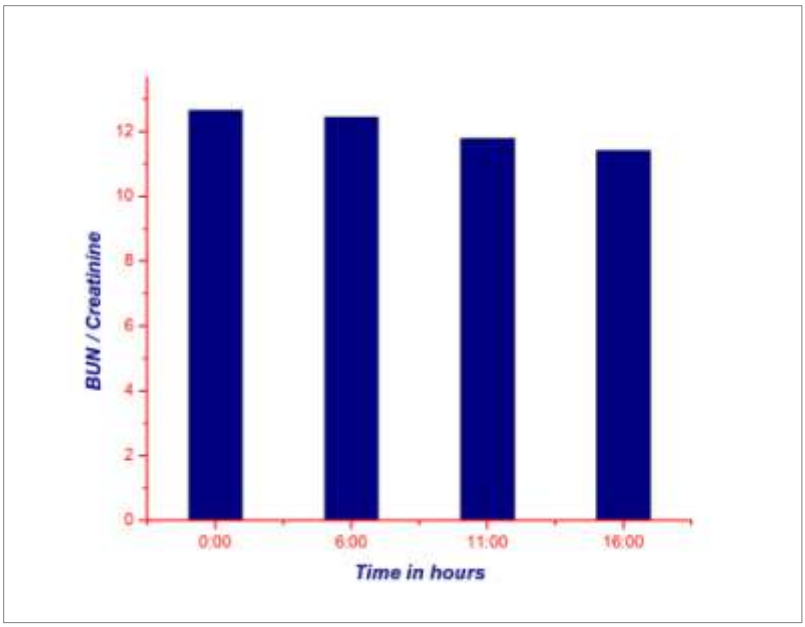

Figure-5: BUN to Creatinine Ratio

When the BUN to Creatinine ratio (BUN:creatinine) is higher (in close proximity to 20), the subject is suspected of having prerenal azotemia i.e. the intrinsic function of kidney is normal but nitrogenous waste are produced as a result of muscle degradation. Since in the current study the BUN/Creatinine ratio was gradually decreasing (but remained within the normal range) with the time, it indicates a depletion in body protein.

4.1.4 Triglyceride and cholesterol level in blood:

The blood cholesterol level did not show much variation (figure not shown) with fatigue development in drivers while triglyceride level (Stage1: 121.5 ± 8.5, Stage2: 143.25 ± 10.6, Stage3: 173.75 ± 14.2, Stage4: 166 ± 5.5) showed a gradual increase (figure-6) indicating continuous release of the later between the meals to compensate energy demand of monotonous exercise.

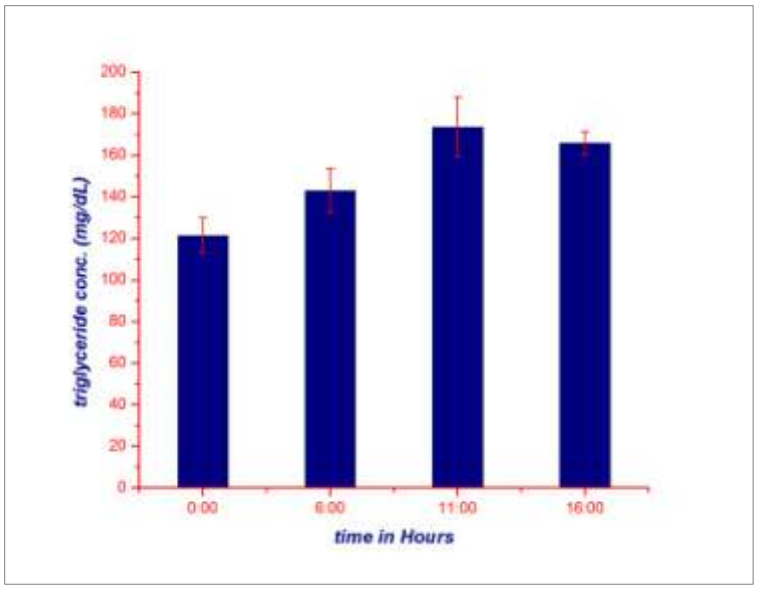

Figure-6: Triglyceride Level in Blood

4.1.5 Total protein Content in blood:

The total protein content did not vary much and remained in the normal range (6.3 to 8.4 gm %). As shown (figure-7) the protein content in blood decreases except the last point which increases a little.

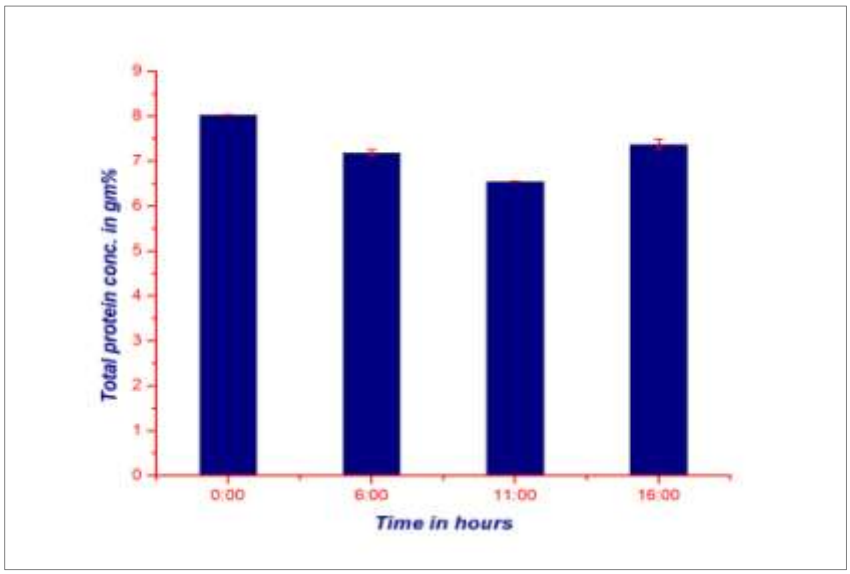

Figure-7: Total protein content in blood

4.2 Subjective assessment

The subjective assessment study was done following three instruments namely

i. SF-36 v2 health survey scoring
ii. Beck Depression Inventory (BDI-II)
iii. Oswestry Disability Questionnaire

4.2.1 SF-36v2 Health Survey

SF-36v2 health survey is one of the most reliable, practical surveys and provides valid information about the patient's health condition. It has two components namely Physical Component Summary (PCS) and Mental Component Summary (MCS). Again these each part consists of some subdivisions. The PCS gives the summary of Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), and General Health (GH). Each of this section consists of few questionnaires. Again coming to MCS, it consists of Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH). The details of the questionnaires is provided in appendix-I. The average result summary is given below.

4.2.1.1 Physical Component Summary (PCS)

4.2.1.1.1 Physical Functioning (PF)

Physical functioning account for multiple tasks completing capability that involves physical movement likely vigorous activities (running, lifting etc.), moderate activities (moving a table, bowling etc.), walking (small distance of hundred yards, medium distance and long distance),

lifting and carrying, climbing , bending , kneeling, self maintenance (bathing, dressing etc.). During the whole period of the experiment, the questionnaires were customized as per our requirement and the scoring was expressed as Mean ± SEM. The score varied from around 50 to a minimum of 25 (Stage1- 51.78±1.59; Stage2- 46.12±2.05, Stage3- 39.12±1.80, Stage4- 25.22±1.16). The value 51.78±1.59 at the starting of the experiment signifies that the subject is able to do the mentioned tasks; whereas, with the gradual progression of the experiment the value decreases drastically signifying the increased disablement of the subject to perform the minimal possible task defined by the system.

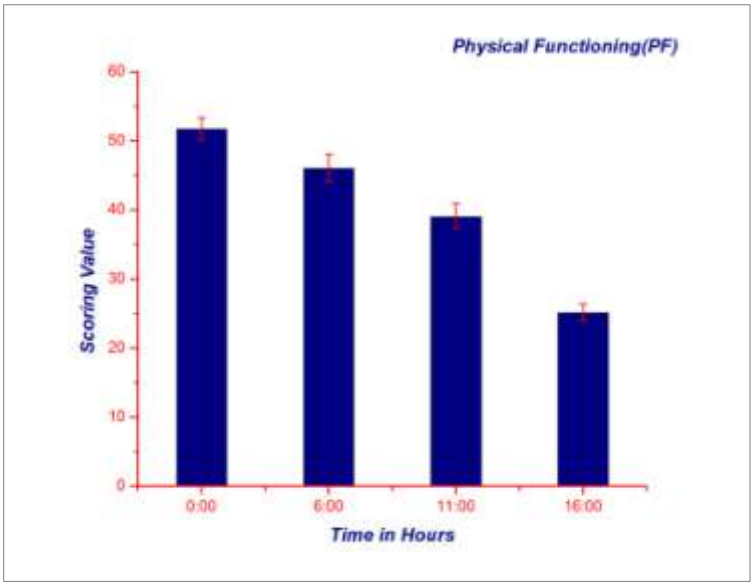

Figure-8: Physical Functioning (PF)

4.2.1.1.2 Role Physical (RP)

This parameter accounts for the ability of the subject to perform the defined task. Role physical enquires about the cut down in the amount of time that the subject spends on a particular activity, the accomplishment time, level of difficulty in performing the work (taking extra effort for a

specific job) etc. The scoring values vary (Stage1- 64.73 ± 0.82, Stage2- 52.80 ± 1.16, Stage3- 38.82 ± 2.16, and Stage4- 32.87 ± 2.25) which are decreasing in a similar to that of Physical functioning.

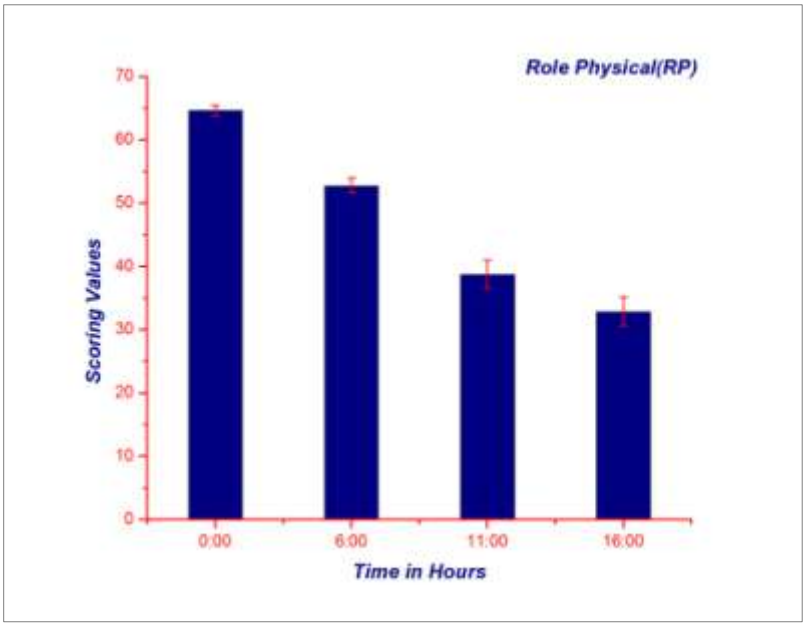

Figure-9: Role Physical (RP)

4.2.1.1.3 Bodily Pain (BP)

Bodily pain strictly accounts for the magnitude of the pain and the obstruction/ interference created by it in the general regular activities during the period of experiment. From the figure-10, the decreasing value of the scoring (Stage1: 50.8 ± 1.1, Stage2: 48.7 ± 1.4, Stage3: 38.5 ± 0.7, Stage4: 35.9 ± 1.1) clearly signifies the increasing extent of pain towards the completion of the experiment.

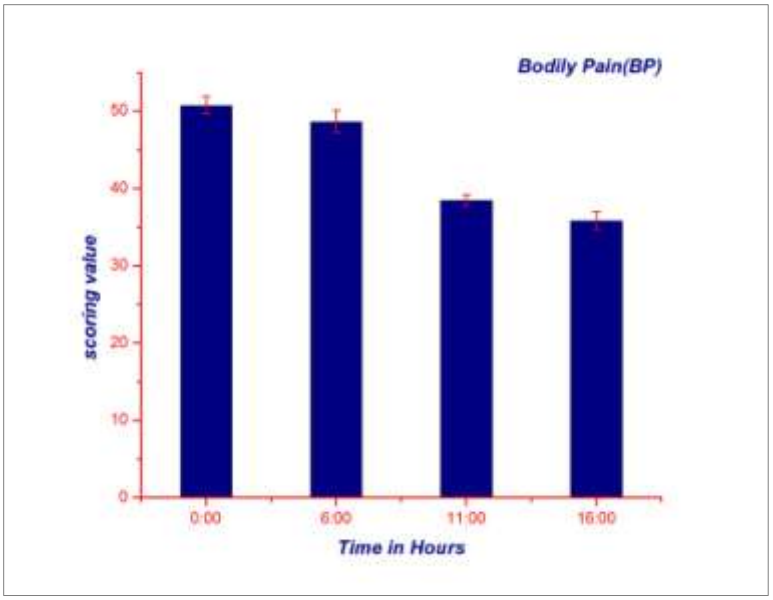

Figure-10: Bodily Pain (BP)

4.2.1.1.4 General Health (GH)

General health mainly concerns regarding the general feeling for the health condition at the moment (feeling of getting sick easily as compared others, expecting the health to get worse in the coming hours, realizing that you are as healthy as your surround people etc.). The scoring values for General Health are Stage1- 68.63 ± 1.24, Stage2- 54.90 ± 0.92, Stage3- 42.08 ± 1.80, and Stage4- 33.85 ± 1.53. The average general health scoring values shows a declining trend along with the progression of fatigue.

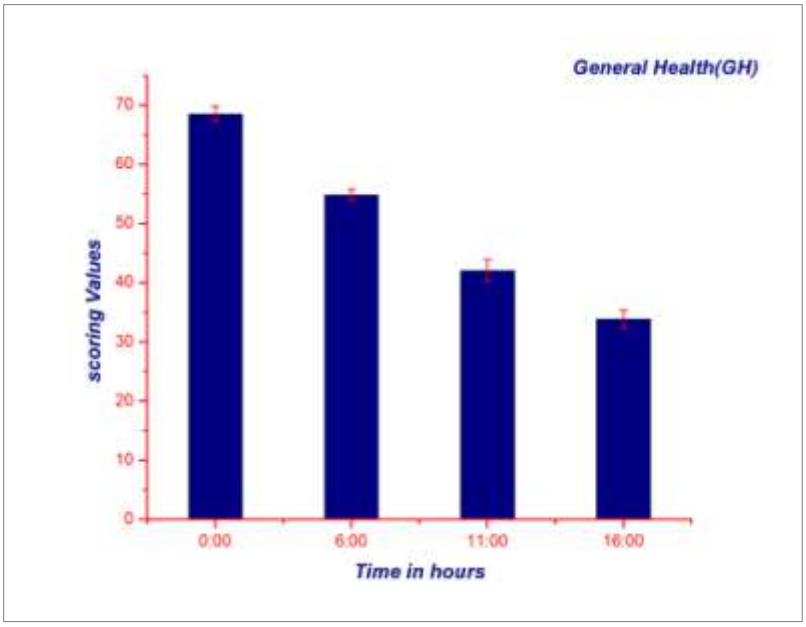

Figure-11: General Health (GH)

On overall analysis the Physical Component Summary (PCS) comes out to be:

All the parameters such as physical functioning (PF), Role-Physical (RP), Bodily Pain (BP), and General Health (GH) that account for the physical health condition at a time point can be summarized under the heading of Physical Component Summary (PCS). The PCS value gradually decreases (Stage1: 60.50 ± 2.1, Stage2: 52.23 ± 1.3, Stage3: 41.52 ± 0.6, Stage4: 33.70 ± 0.3) with the progression of fatigue with an inference that the physical health condition declines with fatigue combined with sleep deprivation.

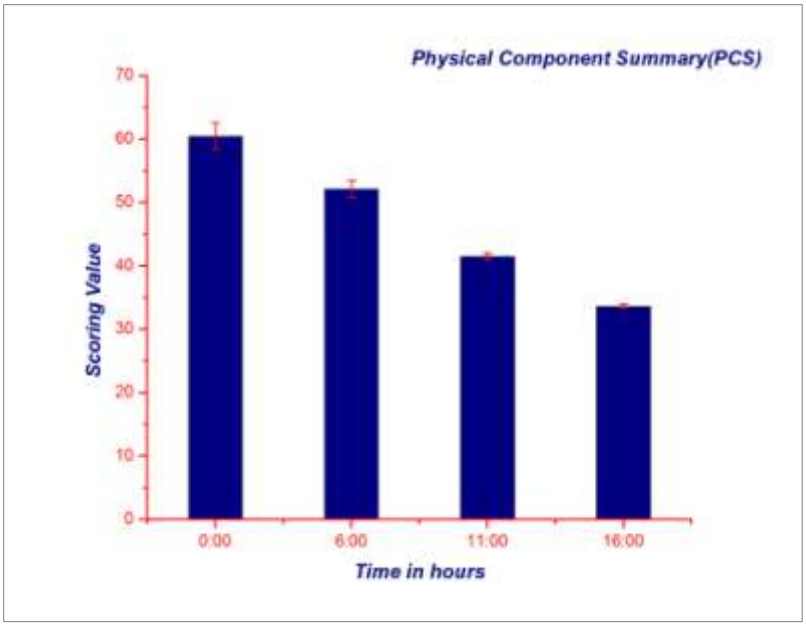

Figure-12: Physical Component Summary (PCS)

4.2.1.2 Mental Component Summary (MCS)

4.2.1.2.1 Vitality (VT)

Vitality is a factor that explains strength and liveliness. This factor is an unseen force that has contribution to both physical as well as mental health condition. The response to the questionnaires in this section reveals the subject's feeling of full of life, any nervousness regarding completing the task, down/dumbness, calm and cheerful, a sense of ineffectiveness, getting exhausted etc. The average scoring was found to be Stage1: 74.1 ± 0.9, Stage2: 60.4 ± 0.9, Stage3: 43.0 ± 0.8, Stage4: 31.5 ± 1.3. It was observed that this vital component was decreasing from 74.1 ± 0.9 (Stage1), at the starting of the experiment which reflects a quite good and healthy condition to 31.5 ± 1.3 (Stage4) which is near to the worst condition. This drastic change signifies a remarkable increase in anxiety and disquiet.

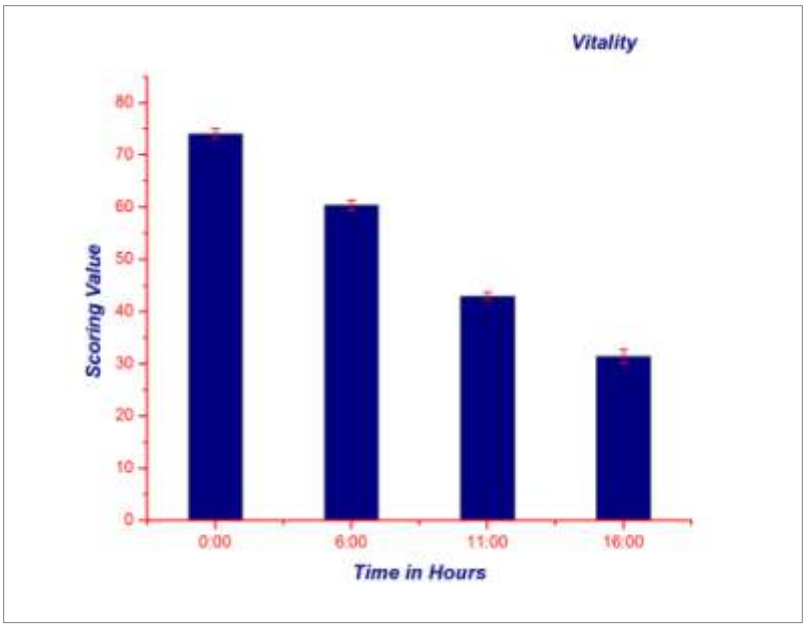

Figure-13: Vitality (VT)

4.2.1.2.2 Social Functioning (SF)

The social functioning (SF) scoring values were decreasing gradually (Stage1: 64.8 ± 0.7, Stage2: 48.7 ± 0.9, Stage3: 43.2 ± 0.9, Stage4: 31.8 ± 1.3) along with the increasing effect of fatigue as shown in figure. The term Social Functioning here refers to the extent of effect of physical health and emotional problems on social life of a being and their duration. From the decreasing value in the Social Functioning the conclusion can be drawn that the subject was losing his interest in social activities at the very point. This might be arising due to annoyance and desperation.

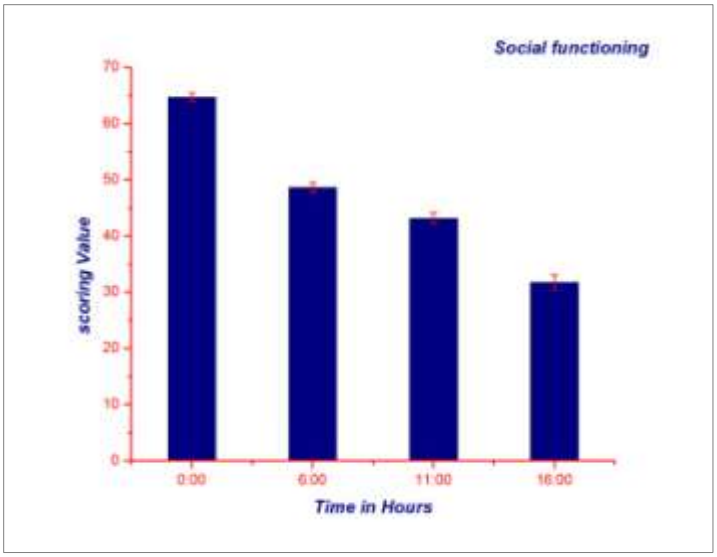

Figure-14: Social Functioning (SF)

4.2.1.2.3 Role Emotional (RE)

Role Emotional (RE) factor deals with the feelings of depression or anxiety and the effect of emotional problems on day-to-day life activity. The scoring value (Stage1: 62.5 ± 1.2, Stage2: 48.8 ± 1.7, Stage3: 38.4 ± 0.7, Stage4: 20.5 ± 1.3) also decreases along with the progression of fatigue, which signifies the increasing level of distress and apprehension for social life.

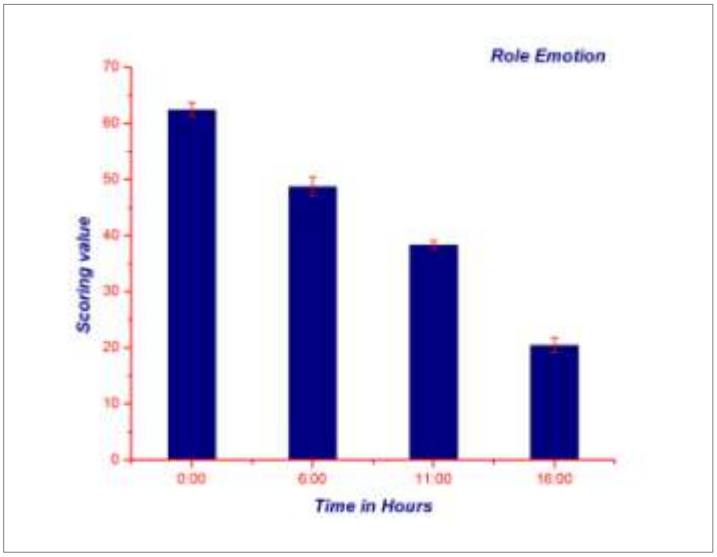

Figure-15: Role Emotion (RE)

4.2.1.2.4 Mental Health (MH)

This factor explains the role and contribution of nervousness, downheartedness, extent of feeling peaceful and happiness on the generation of fatigue. Similar to the other factors, mental health (MH) also decreased (Stage1: 61.7 ± 0.9, Stage2: 50.5 ± 1.1, Stage3: 33.4 ± 1.0, Stage4: 23.0 ± 1.6). This significance decrease in scoring value explains a decline in mental health condition.

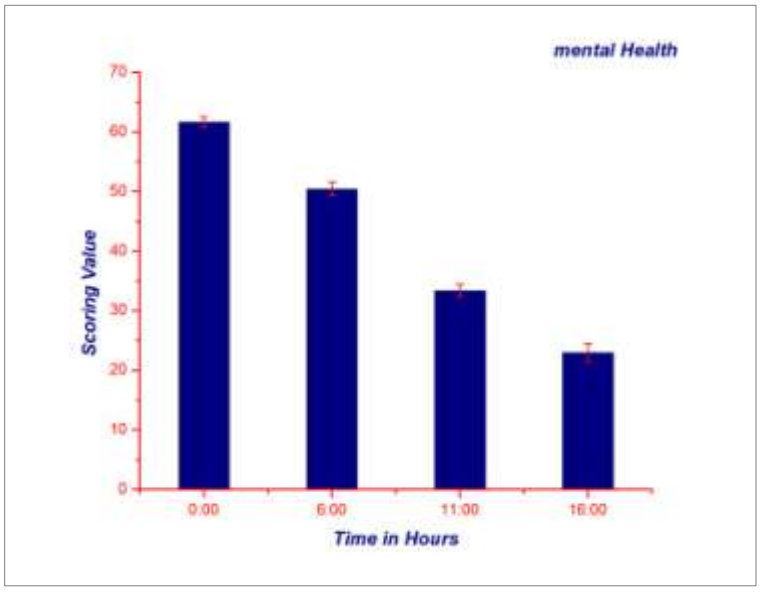

Figure-16: Mental Health (MH)

On overall analysis the Mental Component Summary (MCS) comes out to be:

Aggregating the components such as Vitality (VT), Social Functioning (SF), Role Emotion (RE), Mental Health (MH), an cumulative result comes which is termed as Mental Component Summary (MCS). The average scoring values of MCS (Stage1: 67.4 ± 0.8, Stage2: 52.3 ± 1.1, Stage3: 42.0 ± 0.6, Stage4: 27.5 ± 1.4) shows a declining trend with the progression of fatigue.

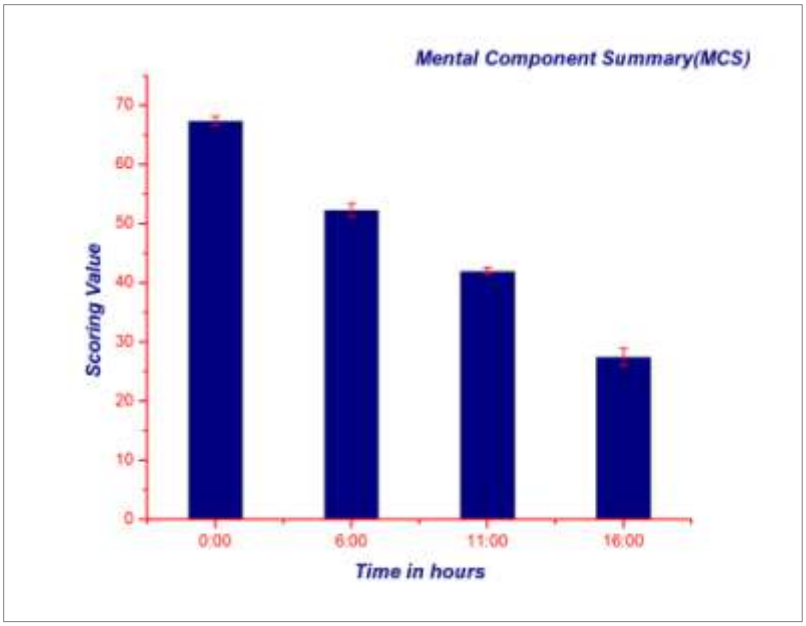

Figure-16: Mental Component Summary (MCS)

From over all analysis of SF36v2; the outcome signifies that there is a substantial decrease in both physical and emotional level as the progression in fatigue occurs.

4.2.2 Beck Depression Inventory (BDI-II)

The scoring is expressed as Mean ±SEM. The average scoring values were found to be (S1: 3.16 ± 0.84, S2: 9 ± 0.52, S3: 14 ± 0.26, S4: 16.8 ± 0.12). The result of all stages is shown in the figure-17.

In Beck Depression Inventory, from psychodynamic prospective, the analysis is done on two factor approach to depression. According to Beck Inventory, Depression can have two components i.e. affective component which contains eight items namely pessimism, feeling of past failure, guiltiness feeling, feeling of punishment, self-dislike, self-criticalness, worthlessness, suicidal thoughts; whereas the somatic component consists of agitation, loss of

pleasure, sadness, crying, loss of energy, loss of interest, indecisiveness, irritability, change in appetite, tiredness, concentration difficulties, change in sleep pattern and loss of interest[22][23]. In most of the subjects it was observed that the scoring was gradually increasing along with the progression of fatigue. It was found that in most of the subjects, the somatic depression was more dominant as compared to the affective depression during towards the completion of the whole task. As we can observe that the percentage change in the mood disturbance over first time point (control) is 184.8%, 158.2%, 88.6% in the successive three stages. The relative decrease in the last stage can be explained by the subject's feeling of assurance that the task is getting over after a prolonged binding to a task. However, all the scoring values were coming under low level of depression (mild mood disturbance) and need not any kind of professional treatment.

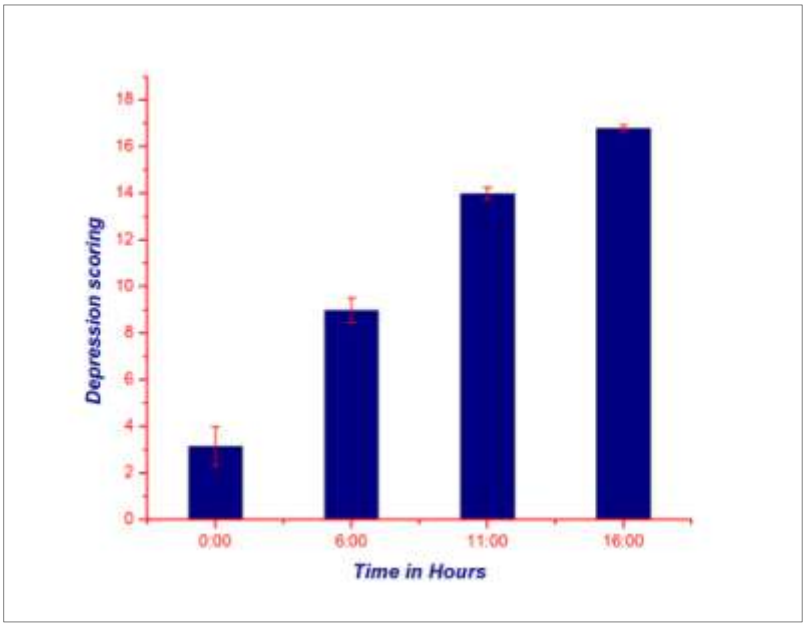

Figure-17: Beck Depression Inventory

4.2.3 Oswestry Disability Questionnaire

In order to know the extent of pain, Oswestry Disability Questionnaire is one of the best methods. This is considered as the golden rules for the evaluation of pain. The scoring was expressed as Mean± SEM. The average scoring was found to be (S1-2.50 ± 0.01 %, S2-5.20±0.01%, S3- 14.30±0.01%, S4- 24.70±0.02%). The increasing score indicates gradual increase in the pain out of fatigue. The scoring also discriminates the different stages of fatigue.

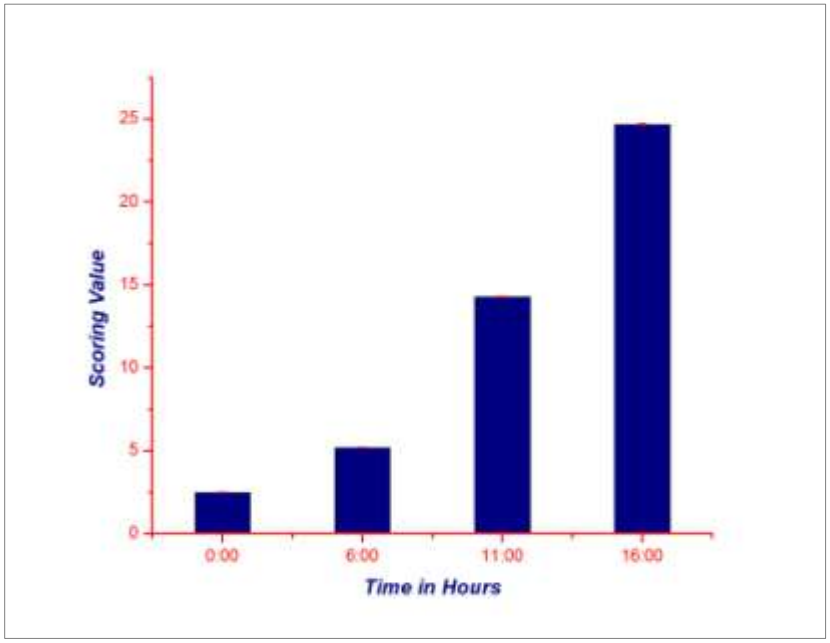

Figure-18: Oswestry Disability Questionnaire

Chapter-5

Conclusion

Drivers fatigue under sleep deprivation consist of multiple factors likely emotional distortion i.e., distraction from the task, despair/depression, exhaustion, lethargy, languorous (feeling of lack of interest or energy), lassitude (lack of vitality or energy), somnolence (a very sleepy state) etc. If fatigue (both motor and cognitive) is combined with sleep deprivation for a prolonged period as occurs in long distance driving, it can lead to psychosomatic pain which in turn can generate substantial depressive feeling in the subjects. In the current study, the various factors (both biochemical and subjective) advocate that with the progression of fatigue multiple parameters alter following a similar trend. The increased creatinine level in blood and the gradual decrease in the BUN/Creatinine ratio signify depletion of muscle protein due to progression of central fatigue and its spread to the periphery for the development of physical fatigue. The gradual increase in Triglyceride concentration may be to compensate the energy demands during progression of fatigue, which goes in support of the above statement. Coming to the psychometric parameters, all are altering following a similar trend. PCS suggest a gradual decline in physical functioning and performance with progression of fatigue. The level of pain was found to be increasing as signified by PCS, which is again supported by the Oswestry Disability Questionnaire. This infers a substantial rate increase in both somatogenic as well as psychogenic pain with the progression of fatigue. The correlation of BDI and Role Emotion gives a value -0.97, which signifies with the decreasing value of Emotional component of MCS the BDI scoring increases proportionally ensuring a considerable increase in the level of depression with progression of fatigue. Since the BDI value is within the limit (< 17%: mild mood disturbance), the subject doesn't require any professional treatment. The significant variation of these parameters (both biochemical and psychometric) suggest that they can be effectively utilized for clinical staging of fatigue.

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APPENDIX-I

(Subjective assessment Questionnaires)

SF36v2™ HEALTH SURVEY SCORING

SF-36v2™ Health Survey Scoring Demonstration

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

---

1. **In general, would you say your health is: [Click on the circle that best describes your answer.]**

Excellent	Very Good	Good	Fair	Poor
○	○	○	○	○

---

2. ***Compared to one year ago,* how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

---

3. **The following questions are about activities you might do during a typical day. *Does your health now limit* you in these activities? If so, how much? [Click on a circle on each line.]**

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a.	*Vigorous Activities,* such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b.	*Moderate Activities,* such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c.	Lifting or carrying groceries	○	○	○
d.	Climbing *several* flights of stairs	○	○	○
e.	Climbing *one* flight of stairs	○	○	○
f.	Bending, kneeling, or stooping	○	○	○
g.	Walking *more than a mile*	○	○	○
h.	Walking *several hundred yards*	○	○	○
i.	Walking *one hundred yards*	○	○	○
j.	Bathing or dressing yourself	○	○	○

4. **During the *past 4 weeks*, how much of the time have you had any of the following problems with your work or other regular daily activities *as a result of your physical health?***

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the *amount of time* you spent on work or other activities	○	○	○	○	○
b. *Accomplished* less than you would like	○	○	○	○	○
c. Were limited in the *kind* of work or other activities	○	○	○	○	○
d. Had *difficulty* performing the work or other activities (for example, it took extra effort)	○	○	○	○	○

5. **During the *past 4 weeks*, how much of the time have you had any of the following problems with your work or other regular daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the *amount of time* you spent on work or other activities	○	○	○	○	○
b. *Accomplished less* than you would like	○	○	○	○	○
c. Did work or activities *less carefully than usual*	○	○	○	○	○

6. **During the *past 4 weeks*, to what *extent* has your *physical health or emotional problems* interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
○	○	○	○	○

7. **How much *bodily* pain have you had during the *past 4 weeks*?**

None	Very Mild	Mild	Moderate	Severe	Very Severe
○	○	○	○	○	○

8. **During the *past 4 weeks*, how much did *pain* interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

9. **These questions are about how you feel and how things have been with you *during the past 4 weeks*. For each question, please give the one answer that comes closest to the way you have been feeling.**

How much of the time during the *past 4 weeks*...

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Did you feel full of life?	○	○	○	○	○
b.	Have you been very nervous?	○	○	○	○	○
c.	Have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○
d.	Have you felt calm and peaceful?	○	○	○	○	○
e.	Did you have a lot of energy?	○	○	○	○	○
f.	Have you felt downhearted and depressed?	○	○	○	○	○
g.	Did you feel worn out?	○	○	○	○	○
h.	Have you been happy?	○	○	○	○	○
i.	Did you feel tired?	○	○	○	○	○

10. **During the *past 4 weeks,* how much of the time has your *physical health or emotional problems* interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

11. **How TRUE or FALSE is *each* of the following statements for you?**

		Definitely true	Mostly true	Don't Know	Mostly false	Definitely false
a.	I seem to get sick a little easier than other people	○	○	○	○	○
b.	I am as healthy as anybody I know	○	○	○	○	○
c.	I expect my health to get worse	○	○	○	○	○
d.	My health is excellent	○	○	○	○	○

Clear Survey | Score the Survey

BECK DEPRESSION INVENTORY-II

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism
0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure
0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure
0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike
0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness
0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying
0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

Continued on Back

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11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

3 4 5 6 7 8 9 10 11 12 A B C D E

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

OSWESTRY DISABILITY QUESTIONNAIRE

Oswestry Disability Questionnaire

This questionnaire has been designed to give us information as to how your back or leg pain is affecting your ability to manage in everyday life. Please answer by checking **one box in each section** for the statement which best applies to you. We realise you may consider that two or more statements in any one section apply but please just shade out the spot that indicates the statement **which most clearly describes your problem.**

Section 1: Pain Intensity

- ☐ I have no pain at the moment
- ☐ The pain is very mild at the moment
- ☐ The pain is moderate at the moment
- ☐ The pain is fairly severe at the moment
- ☐ The pain is very severe at the moment
- ☐ The pain is the worst imaginable at the moment

Section 2: Personal Care (eg. washing, dressing)

- ☐ I can look after myself normally without causing extra pain
- ☐ I can look after myself normally but it causes extra pain
- ☐ It is painful to look after myself and I am slow and careful
- ☐ I need some help but can manage most of my personal care
- ☐ I need help every day in most aspects of self-care
- ☐ I do not get dressed, wash with difficulty and stay in bed

Section 3: Lifting

- ☐ I can lift heavy weights without extra pain
- ☐ I can lift heavy weights but it gives me extra pain
- ☐ Pain prevents me lifting heavy weights off the floor but I can manage if they are conveniently placed eg. on a table
- ☐ Pain prevents me lifting heavy weights but I can manage light to medium weights if they are conveniently positioned
- ☐ I can only lift very light weights
- ☐ I cannot lift or carry anything

Section 4: Walking*

- ☐ Pain does not prevent me walking any distance
- ☐ Pain prevents me from walking more than 2 kilometres
- ☐ Pain prevents me from walking more than 1 kilometre
- ☐ Pain prevents me from walking more than 500 metres
- ☐ I can only walk using a stick or crutches
- ☐ I am in bed most of the time

Section 5: Sitting

- ☐ I can sit in any chair as long as I like
- ☐ I can only sit in my favourite chair as long as I like
- ☐ Pain prevents me sitting more than one hour
- ☐ Pain prevents me from sitting more than 30 minutes
- ☐ Pain prevents me from sitting more than 10 minutes
- ☐ Pain prevents me from sitting at all

Section 6: Standing

- ☐ I can stand as long as I want without extra pain
- ☐ I can stand as long as I want but it gives me extra pain
- ☐ Pain prevents me from standing for more than 1 hour
- ☐ Pain prevents me from standing for more than 30 minutes
- ☐ Pain prevents me from standing for more than 10 minutes
- ☐ Pain prevents me from standing at all

Section 7: Sleeping

- ☐ My sleep is never disturbed by pain
- ☐ My sleep is occasionally disturbed by pain
- ☐ Because of pain I have less than 6 hours sleep
- ☐ Because of pain I have less than 4 hours sleep
- ☐ Because of pain I have less than 2 hours sleep
- ☐ Pain prevents me from sleeping at all

Section 8: Sex Life (if applicable)

- ☐ My sex life is normal and causes no extra pain
- ☐ My sex life is normal but causes some extra pain
- ☐ My sex life is nearly normal but is very painful
- ☐ My sex life is severely restricted by pain
- ☐ My sex life is nearly absent because of pain
- ☐ Pain prevents any sex life at all

Section 9: Social Life

- ☐ My social life is normal and gives me no extra pain
- ☐ My social life is normal but increases the degree of pain
- ☐ Pain has no significant effect on my social life apart from limiting my more energetic interests e.g. sport
- ☐ Pain has restricted my social life and I do not go out as often
- ☐ Pain has restricted my social life to my home
- ☐ I have no social life because of pain

Section 10: Travelling

- ☐ I can travel anywhere without pain
- ☐ I can travel anywhere but it gives me extra pain
- ☐ Pain is bad but I manage journeys over two hours
- ☐ Pain restricts me to journeys of less than one hour
- ☐ Pain restricts me to short necessary journeys under 30 minutes
- ☐ Pain prevents me from travelling except to receive treatment

Score: / **x 100 =** **%**

Scoring: For each section the total possible score is 5: if the first statement is marked the section score = 0, if the last statement is marked it = 5. If all ten sections are completed the score is calculated as follows:

Example:

$$\frac{16 \text{ (total scored)}}{50 \text{ (total possible score)}} \times 100 = 32\%$$

If one section is missed or not applicable the score is calculated:

$$\frac{16 \text{ (total scored)}}{45 \text{ (total possible score)}} \times 100 = 35.5\%$$

Minimum Detectable Change (90% confidence): 10%points (Change of less than this may be attributable to error in the measurement)

Source: Fairbank JCT & Pynsent, PB (2000) The Oswestry Disability Index. *Spine*, 25(22):2940-2953.
Davidson M & Keating J (2001) A comparison of five low back disability questionnaires: reliability and responsiveness. Physical Therapy 2002;82:8-24.

*Note: Distances of 1mile, ½ mile and 100 yards have been replaced by metric distances in the Walking section.

APPENDIX-II

(CONCEPTS AND PRINCIPLES OF BIOCHEMICAL ASSAY)

Blood Glucose assay

Principle: In the presence of enzyme Glucose oxidase, glucose is oxidized to Gluconic acid and hydrogen Peroxide. This hydrogen Peroxide further reacts with phenol and 4-aminoaantipyrine. This occurs due to catalytic action of peroxidase forming a red colored quinonemine dye complex. The intensity of the color formed in the solution is directly proportional to the amount of glucose present in the sample.

$$\textbf{Glucose} + O_2 + H_2O \xrightarrow{\textit{Glucose Oxidase}} \textbf{Gluconate} + H_2O_2$$

$$H_2O_2 + \textbf{4aminoantipyrine} + \textbf{Phenol} \xrightarrow{\textit{Peroxidase}} \textbf{Red Quenoneimine dye} + H_2O$$

Urea Assay

Principle: Urea is hydrolyzed to ammonia and CO_2 in the presence of enzyme Urease. The ammonia formed then reacts with phenolic chromogen and hypochlorite to from green colored complex. The intensity of the color formed is directly proportional to the amount of Urea present in the sample.

$$\textbf{Urea} + H_2O \xrightarrow{\textit{Urease}} \textbf{ammonia} + CO_2$$

$$\textbf{Ammonia} + \textbf{Phenolic Chromogen} + \textbf{Hypochlorite} \longrightarrow \textbf{Green color complex}$$

Creatinine assay

Principle: In the alkaline medium Picric acid react with creatinine to form a orange color complex with the alkaline picrate. Intensity of the color formed is directly proportional to the amount of the creatinine present in the sample.

Creatinine + Aklaline picrate ⟶ **Orange colored Complex**

Triglycerides Assay

Principle: Lipase enzyme hydrolyzes the triglycerides to glycerol and free fatty acids. The glycerol produced, in the presence of Glycerol kinase consumes one ATP to form Glycerol 3 phosphate, which is further oxidized to Dihydroxyacetone phosphate producing H_2O_2. This H_2O_2 in the presence of peroxidase, react with 4AAP and phenol to form a red color dye.

Triglycerides $\xrightarrow{\textit{Lipoprotein Lipase}}$ **Glycerol + Free fatty acids**

Glycerol + ATP $\xrightarrow{\textit{Glycerol Kinase}}$ **Glycerol 3 phosphate + ADP**

Glycerol 3 Phosphate + O_2 $\xrightarrow{\textit{Glycerol 3 Phosphate Oxidase}}$ **dihydroxyacetone phosphate + H_2O_2**

H_2O_2 + 4AAP + phenol $\xrightarrow{\textit{Peroxidase}}$ **Red Quinoneimine dye + H_2O**

Cholesterol Assay

Principle: The cholesterol easters in the presence of Cholesterol easterase hydrolyzes to Cholesterol and Fatty acids. This Cholesterol is oxidized to Cholestenone in the presence of Oxidase enzyme producing H_2O_2. This H_2O_2 produced react with 4AAP and phenol forming a Red Quinoneimine dye. The amount of the Cholesterol present is directly proportional to the intensity of the color of the solution.

$$\text{Cholesterol easters} + H_2O \xrightarrow{\textit{Cholesterol Easterase}} \text{Cholesterol} + \text{Fatty Acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\textit{Cholesterol Oxidase}} \text{Cholestenone} + H_2O_2$$

$$H_2O_2 + \text{4AAP} + \text{Phenol} \longrightarrow \text{Red Quinoneimine dye} + H_2O$$

Total Protein Assay:

Principle: Under alkaline pH condition, protein reacts with cupric ions producing a blue color complex. This colored complex absorbs light at 546nm. The amount of protein present is directly proportional to the intensity of color produced.

$$\textbf{Proteins} \xrightarrow[\textit{Alkaline pH}]{\textit{Cu}^{2+}} \textbf{Blue Color Complex}$$